

FORM PFO-1390 (Modified)
(REV 11-2000)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

216008US0PCT

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

09/926679

INTERNATIONAL APPLICATION NO.

PCT/JP00/03340

INTERNATIONAL FILING DATE

24 May 2000

PRIORITY DATE CLAIMED

31 May 1999

TITLE OF INVENTION

ANTIFUNGAL COMBINATION USE

APPLICANT(S) FOR DO/EO/US

Fumiaki IKEDA, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☒ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☐ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

PC/IB/304**PCT/IB/308****Notice of Priority****Request for Consideration of Documents Cited in the International Search Report**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

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INTERNATIONAL APPLICATION NO.

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24. The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

- ☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1040.00
- ☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$890.00
- ☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$740.00
- ☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00
- ☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =**\$890.00**

Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).

\$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	9 - 20 =	0	x \$18.00
Independent claims	1 - 3 =	0	x \$84.00

\$0.00**\$0.00**Multiple Dependent Claims (check if applicable). ☐**\$0.00****TOTAL OF ABOVE CALCULATIONS =****\$890.00**

☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.

\$0.00**SUBTOTAL =****\$890.00**

Processing fee of \$130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).

\$0.00**TOTAL NATIONAL FEE =****\$890.00**

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). ☐

\$0.00**TOTAL FEES ENCLOSED =****\$890.00**

Amount to be:

refunded

\$

charged

\$

- a. ☒ A check in the amount of \$890.00 to cover the above fees is enclosed.
- b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 15-0030. A duplicate copy of this sheet is enclosed.
- d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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24,618

REGISTRATION NUMBER

DATE

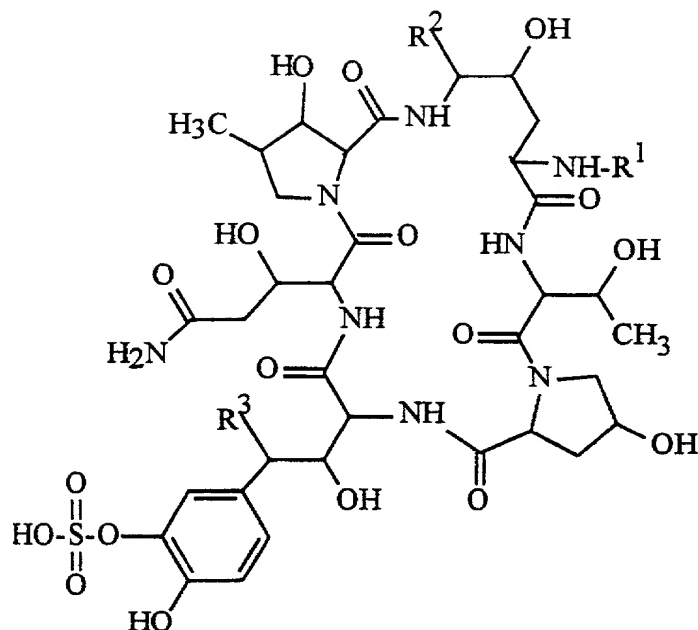
Nov. 30 2001

DESCRIPTION

ANTIFUNGAL COMBINATION USE

5 TECHNICAL FIELD

The present invention relates to antifungal combination use of known antifungal agents such as the azoles, polyenes and so on in combination with a lipopeptide compound antifungal agent. More particularly,
10 the invention relates to antifungal combination use of azoles such as fluconazole (hereinafter referred to as FLCZ), voriconazole, itraconazole (hereinafter referred to as ITCZ), ketoconazole, miconazole, ER 30346 and SCH 56592; polyenes such as amphotericin B (hereinafter referred to as
15 AMPH-B), nystatin, liposomal and lipid forms thereof such as Abelcet, AmBisome and Amphocil; purine or pyrimidine nucleotide inhibitors such as flucytosine (hereinafter referred to as 5-FC); or polyoxins such as nikkomycins, in particular nikkomycin Z or nikkomycin X; other chitin
20 inhibitors; elongation factor inhibitors such as sordarin and analogs thereof; mannan inhibitors such as predamycin, bactericidal/permeability-inducing (BPI) protein products such as XMP.97 or XMP.127; or complex carbohydrate antifungal agents such as CAN-296; with a lipopeptide
25 compound [I] of the following formula:



[I]

Wherein R¹ is acyl group,
 R² is hydrogen or hydroxy and
 R³ is hydrogen or hydroxy,
 or a salt thereof.

BACKGROUND ART

There is an increasing need for agents which are effective against opportunistic mycotic infections by such agents as *Cryptococcus*, *Candida*, *Aspergillus*, *Histoplasma*, *Coccidioides*, *Paracoccidioides*, *Blastomyces*, *Fusarium*, *Sporothrix*, *Trichosporon*, *Rhizopus*, *Pseudallescheria*, dermatophytes, *Paecilomyces*, *Alternaria*, *Curvularia*, *Exophiala*, *Wangiella*, *Penicillium*, *Saccharomyces*, *Dematiaceous* fungi, *Pneumocystis carinii* and so on. The present uses, i.e., polyenes, such as amphotericin B, cause severe side effects and azoles, such as fluconazole, are only fungistatic. The lipopeptide compound [I] is cyclic hexapeptide which inhibits cell wall 1,3 β -D-glucan synthesis. The lipopeptide compound [I] has shown potent *in vivo*

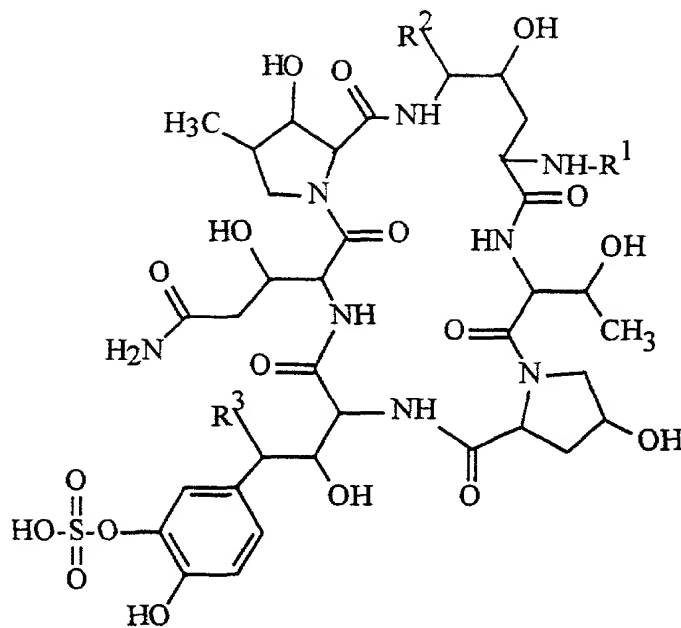
activity against *Candida*, *Pneumocystis carinii*, *Aspergillus*, as well as the other fungal pathogens listed above.

Combination use with antifungal drugs may provide additional options for treating *Aspergillus* and other
5 fungal pathogens.

Previous studies have evaluated the efficacy of other lipopeptide compounds against *Cryptococcus neoformans* in combination with amphotericin B and fluconazole (Abruzzo et al., Antimicrob. Agents Chemo. 1995, 39:1077-1081 and
10 Bartizal et al., Antimicrob. Agents Chemo. 1995, 39:1070-1076). However, none of these studies have demonstrated the results found using the lipopeptide compound [I].

DISCLOSURE OF THE INVENTION

15 The present invention relates to antifungal combination use of known antifungal agents such as the azoles, polyenes and so on in combination with a lipopeptide compound antifungal agent. More particularly, the present invention relates to antifungal combination use
20 of azoles such as fluconazole, voriconazole, itraconazole, ketoconazole, miconazole, ER 30346 and SCH 56592; polyenes such as amphotericin B, nystatin, liposomal and lipid forms thereof such as Abelcet, AmBisome and Amphocil; purine or pyrimidine nucleotide inhibitors such as flucytosine; or
25 polyoxins such as nikkomycins, in particular nikkomycin Z or nikkomycin X; other chitin inhibitors; elongation factor inhibitors such as sordarin and analogs thereof; mannan inhibitors such as predamycin, bactericidal/permeability-inducing (BPI) protein products such as XMP.97 or XMP.127;
30 or complex carbohydrate antifungal agents such as CAN-296; with a lipopeptide compound [I] of the following formula:



[I]

Wherein R^1 is acyl group,

R^2 is hydrogen or hydroxy and

R^3 is hydrogen or hydroxy,

5 or a salt thereof.

Suitable salt of the lipopeptide compound [I] is a pharmaceutically acceptable and conventional non-toxic salt, and may include a salt with a base or an acid addition salt
 10 such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt;

a salt with an organic base, for example, an organic amine
 15 salt (e.g., triethylamine salt, diisopropylethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.);

an inorganic acid addition salt (e.g., hydrochloride
 20 hydrobromide, sulfate, phosphate, etc.);

an organic carboxylic sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.);

5 a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

It is to be noted that each of the lipopeptide compound [I] may include one or more stereoisomer(s) such
10 as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s), and all such isomer(s) and the mixture thereof are included within the scope of the present invention.

The lipopeptide compound [I] or a salt thereof
15 includes solvated compound [e.g., enclosure compound (e.g., hydrate, etc.)].

The lipopeptide compound [I] or a salt thereof includes both its crystal form and non-crystal form.

It should be understood that the lipopeptide compound
20 [I] in the present invention may include the prodrug form.

Suitable example of "acyl group" may include aliphatic acyl, aromatic acyl, arylaliphatic acyl and heterocyclic-
aliphatic acyl derived from carboxylic acid, carbonic acid,
25 carbamic acid, sulfonic acid, and the like.

Suitable example of said "acyl group" may be illustrated as follows.

Aliphatic acyl such as lower or higher alkanoyl (e.g.,
30 formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl,
35 etc.);

lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.);

5 lower or higher alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.);

lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.); or the like;

Aromatic acyl such as

10 aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.); aroyl which has one or more suitable substituent(s); ar(lower)alkanoyl [e.g., phenyl(C₁-C₆)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(C₁-C₆)alkanoyl (e.g., naphthylacetyl,

15 naphthylpropanoyl, naphthylbutanoyl, etc.), etc.]; ar(lower)alkenoyl [e.g., phenyl(C₃-C₆)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentanoyl, phenylhexenoyl, etc.), naphthyl(C₃-C₆)alkenoyl (e.g., naphthylpropenoyl,

20 naphthylbutenoyl, etc.), etc.]; ar(lower)alkoxycarbonyl [e.g., phenyl(C₁-C₆)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), fluorenyl(C₁-C₆)alkoxy-carbonyl (e.g., fluorenylmethyloxycarbonyl, etc.), etc.];

25 aryloxycarbonyl (e.g., phenoxycarbonyl, naphthylloxycarbonyl, etc.); aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.);

30 arylcarbamoyl (e.g., phenylcarbamoyl, etc.); arylthiocarbamoyl (e.g., phenylthiocarbamoyl, etc.); arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.);

arylsulfonyl which may have 1 to 4 lower alkyl (e.g., phenylsulfonyl, p-tolylsulfonyl, etc.); or the like;

Heterocyclic acyl such as

heterocycliccarbonyl; heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, etc.);

- 5 heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, etc.);
heterocyclicglyoxyloyl; or the like.

- 10 Among them, more preferred "acyl group" is aroyl which has one or more suitable substituent(s).

- Suitable example of "suitable substituent(s)" in the term of "aroyl which has one or more suitable substituent(s)" may be heterocyclic group substituted with
15 aryl having lower alkoxy, heterocyclic group substituted with aryl having lower alkoxy(lower)alkoxy, heterocyclic group substituted with aryl having lower alkoxy(higher)alkoxy, heterocyclic group substituted with aryl having cyclo(lower)alkoxy, heterocyclic group
20 substituted with aryl having heterocyclic group, heterocyclic group substituted with cyclo(lower)alkyl having cyclo(lower)alkyl, heterocyclic group substituted with aryl having aryl substituted with lower alkoxy(lower)alkoxy, heterocyclic group substituted with
25 aryl having heterocyclic group substituted with cyclo(lower)alkyl;

- in which the preferred one may be unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl
30 having (C₄-C₆)alkoxy, unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₄-C₆)alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen
35 atom(s) substituted with phenyl having (C₁-C₄)alkoxy-

- (C₄-C₆)alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy, saturated 3 to 8-membered heteromonocyclic
- 5 group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy, unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having cyclo(C₄-C₆)alkoxy, unsaturated condensed
- 10 heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), saturated 3 to 8-membered heteromonocyclic group containing 1 to 4
- 15 nitrogen atom(s) substituted with cyclo(C₄-C₆)alkyl having cyclo(C₄-C₆)alkyl, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having phenyl substituted with (C₁-C₄)alkoxy(C₁-C₄)alkoxy,
- 20 unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo(C₄-C₆)alkyl, unsaturated
- 25 condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) having cyclo(C₄-C₆)alkyl, etc.
- 30 Among them, the most preferred one may be isoxazolyl substituted with phenyl having pentyloxy, imidazothiadiazolyl substituted with phenyl having pentyloxy, thiadiazolyl substituted with phenyl having methoxyhexyloxy, thiadiazolyl substituted with phenyl
- 35 having methoxyoctyloxy, thiadiazolyl substituted with

phenyl having methoxyheptyloxy, imidazothiadiazolyl
substituted with phenyl having cyclohexyloxy,
imidazothiadiazolyl substituted with phenyl having
dimethylmorpholino, piperazinyl substituted with phenyl
5 having methoxyheptyloxy, piperazinyl substituted with
phenyl having methoxyoctyloxy, piperazinyl substituted with
cyclohexyl having cyclohexyl, thiadiazolyl substituted with
phenyl having phenyl substituted with methoxyethoxy,
thiadiazolyl substituted with phenyl having phenyl
10 substituted with methoxybutoxy, thiadiazolyl substituted
with phenyl having phenyl substituted with ethoxypropoxy,
imidazothiadiazolyl substituted with phenyl having
piperazinyl substituted with cyclohexyl,
imidazothiadiazolyl substituted with phenyl having
15 piperazinyl substituted with cyclohexyl.

The more suitable example of "acyl group" of R¹ may be
benzoyl which has isoxazolyl substituted with phenyl having
pentyloxy, benzoyl which has imidazolthiadiazolyl
20 substituted with phenyl having pentyloxy, benzoyl which has
thiadiazolyl substituted with phenyl having methoxyhexyloxy,
benzoyl which has thiadiazolyl substituted with phenyl
having methoxyoctyloxy, benzoyl which has thiadiazolyl
substituted with phenyl having methoxyheptyloxy, benzoyl
25 which has imidazothiadiazolyl substituted with phenyl
having cyclohexyloxy, benzoyl which has imidazothiadiazolyl
substituted with phenyl having dimethylmorpholino, benzoyl
which has piperazinyl substituted with phenyl having
methoxyheptyloxy, benzoyl which has piperazinyl substituted
30 with phenyl having methoxyoctyloxy, benzoyl which has
piperazinyl substituted with cyclohexyl having cyclohexyl,
benzoyl which has thiadiazolyl substituted with phenyl
having phenyl substituted with methoxyethoxy, benzoyl which
has thiadiazolyl substituted with phenyl having phenyl
35 substituted with methoxybutoxy, benzoyl which has

thiadiazolyl substituted with phenyl having phenyl
substituted with ethoxypropoxy, benzoyl which has
imidazothiadiazolyl substituted with phenyl having
piperazinyl substituted with cyclohexyl, benzoyl which has
5 imidazothiadiazolyl substituted with phenyl having
piperazinyl substituted with cyclohexyl.

The lipopeptide compound [I], its preparation, its
dosage, etc. are disclosed in U.S. Patent Nos. 5,376,634,
10 5,569,946 and WO96/11210, the disclosures of which are
incorporated herein by reference.

The azole, polyene or other antifungal agent may be
administered orally or parenterally. The lipopeptide
compound [I] is preferably administered parenterally, but
15 is not limited to that route, and may also be administered
by other routes such as oral, intramuscular or subcutaneous,
and may be administered simultaneously, separately,
sequentially in combination with the azole, polyene or
other antifungal agent.

20 In more details, the antifungal combination use of the
present invention is effective, particularly against the
following fungi.

Acremonium;

Absidia (e.g., *Absidia corymbifera*, etc);

25 *Aspergillus* (e.g., *Aspergillus clavatus*, *Aspergillus*
flavus, *Aspergillus fumigatus*, *Aspergillus nidulans*,
Aspergillus niger, *Aspergillus terreus*, *Aspergillus*
versicolor, etc);

Blastomyces (e.g., *Blastomyces dermatitidis*, etc);

30 *Candida* (e.g., *Candida albicans*, *Candida glabrata*,
Candida guilliermondii, *Candida kefyr*, *Candida*
krusei, *Candida parapsilosis*, *Candida stellatoidea*, *Candida*
tropicalis, *Candida utilis*, etc.);

Cladosporium (e.g., *Cladosporium trichoides*, etc);

35 *Coccidioides* (e.g., *Coccidioides immitis*, etc);

Cryptococcus (e.g., *Cryptococcus neoformans*, etc);
Cunninghamella (e.g., *Cunninghamella elegans*, etc);
 Dermatophyte;
Exophiala (e.g., *Exophiala dermatitidis*, *Exophiala*
 5 *spinifera*, etc);
Epidermophyton (e.g., *Epidermophyton floccosum*, etc);
Fonsecaea (e.g., *Fonsecaea pedrosoi*, etc);
Fusarium (e.g., *Fusarium solani*, etc);
Geotrichum (e.g., *Geotrichum candidum*, etc);
 10 *Histoplasma* (e.g., *Histoplasma capsulatum* var.
capsulatum, etc);
Malassezia (e.g., *Malassezia furfur*, etc);
Microsporum (e.g., *Microsporum canis*, *Microsporum*
gypseum, etc);
 15 *Mucor*;
Paracoccidioides (e.g., *Paracoccidioides*
brasiliensis, etc);
Penicillium (e.g., *Penicillium marneffei*, etc);
Phialophora;
 20 *Pneumocystis* (e.g., *Pneumocystis carinii*, etc);
Pseudallescheria (e.g., *Pseudallescheria boydii*, etc);
Rhizopus (e.g., *Rhizopus microsporus* var.
rhizopodiformis, *Rhizopus oryzae*, etc);
Saccharomyces (e.g., *Saccharomyces cerevisiae*, etc);
 25 *Scopulariopsis*;
Sporothrix (e.g., *Sporothrix schenckii*, etc);
Trichophyton (e.g., *Trichophyton mentagrophytes*,
Trichophyton rubrum, etc);
Trichosporon (e.g., *Trichosporon asahii*, *Trichosporon*
 30 *cutaneum*, etc).

The above fungi are well known to cause various
 infection diseases in skin, hair, nail, oral mucosa,
 gastrointestinal tract, bronchus, lung, endocardium, brain,
 meninges, urinary organ, vaginal protion, oral cavity,
 35 ophthalmus, systemic, kidney, bronchus, heart, external

auditory canal, bone, nasal cavity, paranasal cavity, spleen, liver, hypodermal tissue, lymph duct, gastrointestinal, articulation, muscle, tendon, interstitial plasma cell in lung, and so on.

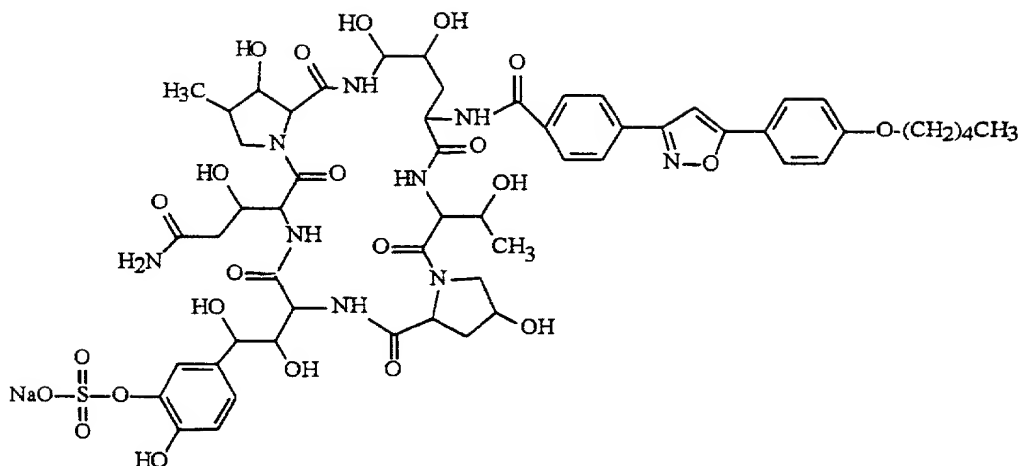
Therefore, the combination use of the present invention are useful for preventing and treating various infectious diseases, such as dermatophytosis (e.g., trichophytosis, etc), pityriasis versicolor, candidiasis, cryptococcosis, geotrichosis, trichosporosis, aspergillosis, penicilliosis, fusariosis, zygomycosis, sporotrichosis, chromomycosis, coccidioidomycosis, histoplasmosis, blastomycosis, paracoccidioidomycosis, pseudallescheriosis, mycetoma, mycotic keratitis, otomycosis, pneumocystosis, and so on.

The invention is further described in connection with the following non-limiting examples.

30

35

EXAMPLES

Test Compound

Test Method

The broth microdilution method using RPMI medium (pH7.0) was used, comparing the each drug alone (Test Compound, AMPH-B, ITCZ, Nikkomycin X and 5-FC) and combined for each clinical isolates of *Aspergillus fumigatus*. A combination of drug concentrations was evaluated by the checkerboarded method.

All tubes were examined macroscopically for growth and compared to a control (no drug). MIC was visually determined as the lowest concentration resulting in prominent decrease in turbidity compared to controls.

The Fractional Inhibitory Concentration(FIC) for each drug in mixture wells was compared to the MIC for each drug alone. The FIC index was calculated from the sum of the FICs for the two drugs. A quantitative expression of the interaction for inhibition is as follows:

$$\text{Synergy} \leq 0.5;$$

Test Result

In vitro combination with Test Compound and AMPH-B against *A. fumigatus*

Organism	MIC ($\mu\text{g/mL}$)				FIC index
	Test Compound Alone	Test Compound Combination	AMPH-B alone	AMPH-B combination	
<i>A. fumigatus</i> 8004	0.0313	0.0078	2	0.5	0.50

5

In vitro combination with Test Compound and ITCZ against *A. fumigatus*

Organism	MIC ($\mu\text{g/mL}$)				FIC index
	Test Compound Alone	Test Compound combination	ITCZ alone	ITCZ combination	
<i>A. fumigatus</i> 8008	0.0313	0.0078	0.5	0.125	0.50

10

In vitro combination with Test Compound and Nikkomycin X against *A. fumigatus*

Organism	MIC ($\mu\text{g/mL}$)				FIC index
	Test Compound Alone	Test Compound combination	Nikkomycin X alone	Nikkomycin X combination	
<i>A. fumigatus</i> FP1923	0.0039	≤ 0.001	128	4	0.28

15

In vitro combination with Test Compound and 5-FC against *A. fumigatus*

Organism	MIC ($\mu\text{g/mL}$)				FIC index
	Test Compound Alone	Test Compound combination	5-FC alone	5-FC combination	
<i>A. fumigatus</i> FP1990	0.0078	0.002	>32	8	0.38

5 From the results of the above example, synergy effect of efficacy was observed with combination of the lipopeptide compound [I] and amphotericin B, itraconazole, Nikkomycin X or 5-FC at certain concentrations. No antagonism of efficacy with amphotericin B, itraconazole, 10 Nikkomycin X or 5-FC in combination with the lipopeptide compound [I] also was seen.

We also have examined in vitro combination with the lipopeptide compound [I] and amphotericin B or itraconazole against other fungi such as *C. albicans*, *C. neoformans* and 15 so on. From the result, synergy effect of efficacy was observed with such combination use.

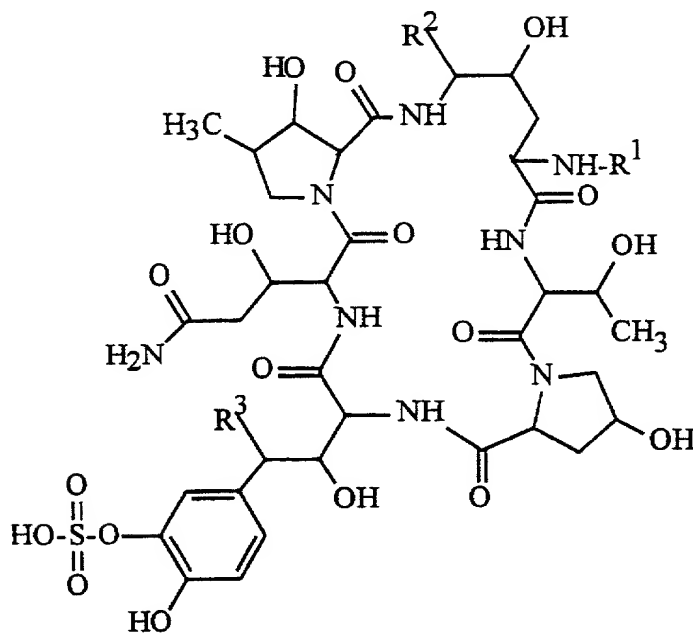
Given the above disclosure, it is confirmed that combination using various antifungal agents and the lipopeptide compound [I] is effective against fungal 20 infections caused by the fungal pathogens. Accordingly, it is intended that the above examples should be construed as illustrative and that the invention disclosed herein should be limited only by the following claims.

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CLAIMS

1. A method for treatment or inhibition of the infectious diseases caused by the fungal pathogen which comprises administering an effective amount of a lipopeptide compound [I] of the following formula:



[I]

Wherein R^1 is acyl group,

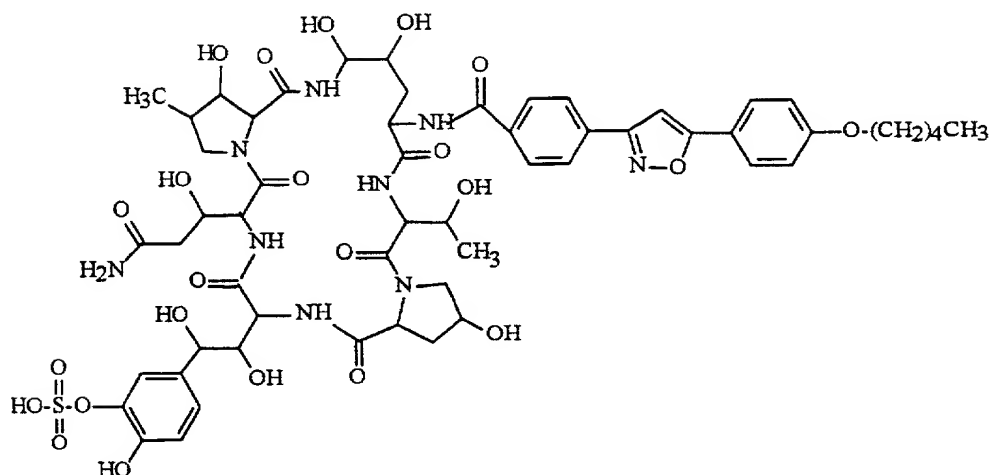
R^2 is hydrogen or hydroxy and

R^3 is hydrogen or hydroxy,

or a salt thereof, in combination with an azole, polyene, purine nucleotide inhibitor, pyrimidine nucleotide inhibitor, mannan inhibitor, protein elongation factor inhibitor, bactericidal/permeability inducing protein product or polyoxin.

2. The method of Claim 1 which comprises administering an effective amount of a lipopeptide compound [I] in combination with a polyene, an azole, a pyrimidine nucleotide inhibitor or polyoxin.

3. The method of Claim 1 wherein the lipopeptide compound [I] is



5 or a salt thereof.

4. The method of Claim 1 wherein the azole is selected from the group consisting of fluconazole, voriconazole, itraconazole, ketoconazole, miconazole, ER 30346, SCH 56592; the polyenes is selected from the group consisting of amphotericin B, nystatin or liposomal and lipid forms thereof; the purine or pyrimidine nucleotide inhibitors is flucytosine; the polyoxin is nikkomycin X, the elongation factor inhibitor is sordarin and analogs thereof and the mannan inhibitor is predamycin.

5. The method of Claim 4 wherein the polyene is Amphotericin B, the azole is Fluconazole or Itraconazole, the pyrimidine nucleotide inhibitor is Flucytosine, and the polyoxin is Nikkomycin X.

6. The method of Claim 1 wherein the infectious diseases are caused by a fungal pathogen selected from

Cryptococcus, Candida, Aspergillus, Histoplasma, Coccidioides, Paracoccidioides, Blastomyces, Fusarium, Sporothrix, Trichosporon, Rhizopus, Pseudallescheria, dermatophytes, Paecilomyces, Alternaria, Curvularia, Exophiala, Wangiella, Penicillium, Saccharomyces, Dematiaceous fungi or Pneumocystis carinii.

7. The method of Claim 6 wherein the fungal pathogen is selected from *Cryptococcus, Candida* or *Aspergillus*.

8. A pharmaceutical composition for the prophylactic and/or therapeutic treatment of the infectious diseases caused by the fungal pathogen which comprises the lipopeptide compound [I] in claim 1 in combination with an azole, polyene, purine nucleotide inhibitor, pyrimidine nucleotide inhibitor, mannan inhibitor, protein elongation factor inhibitor, bactericidal/permeability inducing protein product or polyoxin and optionally pharmaceutically carriers or excipients.

9. Use of the lipopeptide compound [I] in claim 1 for the manufacture of medicament for simultaneous, separate or sequential use for the prevention and/or treatment of the infectious diseases caused by the fungal pathogen in combination with an azole, polyene, purine nucleotide inhibitor, pyrimidine nucleotide inhibitor, mannan inhibitor, protein elongation factor inhibitor, bactericidal/permeability inducing protein product or polyoxin.

Declaration, Power Of Attorney and Petition

Page 1 of 3

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

ANTIFUNGAL COMBINATION USE

the specification of which

☐ is attached hereto.

☐ was filed on _____ as
Application Serial No. _____
and amended on _____.

☐ was filed as PCT international application

Number PCT/JP00/03340
on May 24, 2000,
and was amended under PCT Article 19
on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
PQ0663	Australia	31/05/99	<input type="checkbox"/> Yes <input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

_____	_____
(Application Number)	(Filing Date)
_____	_____
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)
<u>PCT/JP00/03340</u>	<u>May 24, 2000</u>	_____
_____	_____	_____
_____	_____	_____

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; William E. Beaumont, Reg. No. 30,996; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Jeffrey B. McIntyre, Reg. No. 36,867; William T. Enos, Reg. No. 33,128; Michael E. McCabe, Jr., Reg. No. 37,182; Bradley D. Lytle, Reg. No. 40,073; and Michael R. Casey, Reg. No. 40,294; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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